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REMARKS

Rejection of Claims 16-21 and 26-30 Under 35 U.S.C. § 102(e), or Alternatively, Under 35 U.S.C. § 103 (Item 4 of Office Action)

Claims 16-21 and 26-30 have been rejected under 35 U.S.C. § 102(e), or alternatively under 35 U.S.C. § 103, as they are said to be anticipated by, or obvious over, Stamler *et al.* (US 6,538,113).

US 6,538,113 describes a method that was said to result in SNO-hemoglobin. However, this method is described so incompletely that one of ordinary skill in the art could not follow the protocol. No method of assay is described that could measure whether any SNO-hemoglobin had been formed. The method is merely hypothetical; no evidence is given that SNO-hemoglobin was actually produced, and no physiological effect of SNO-hemoglobin was measured. See the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 mailed to the United States Patent and Trademark Office on February 27, 1998, regarding WO 93/09806, which has the same content as US 6,538,113, except for the claims. See Example 19. See also the Declaration of Joseph Bonaventura Under 37 C.F.R. § 1.132 mailed to the U.S. Patent and Trademark Office on March 12, 1998.

WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin, for reasons stated in the Declaration. Therefore, US 6,538,113 also does not present an enabling description of a method to produce S-nitrosohemoglobin. No other reference available at the time of the invention describes a method of producing S-nitrosohemoglobin. Thus, there is no basis for this rejection, either as an anticipation rejection, or as an obviousness rejection. If one of ordinary skill in the art would not know how to make SNO-hemoglobin, then one of ordinary skill in the art could not think of using it in a method of therapy for any purpose.

Rejection of Claims 18-21 and 26-30 Under 35 U.S.C. § 102(e), or Alternatively, Under 35 U.S.C. § 103 (Item 5 of Office Action)

Claims 18-21 and 26-30 have been rejected under 35 U.S.C. § 102(e) as being anticipated, or alternatively, under 35 U.S.C. § 103, as being obvious over Stamler *et al.* (US Patent No. 6,471,978).

Stamler *et al.* (US Patent No. 6,471,978) describe medical devices coated with a nitric oxide adduct. Among the nitric oxide adducts recited for use in the medical devices are S-nitroso-proteins. US Patent No. 6,471,978 describes methods of producing S-nitroso-proteins at column 19, lines 6-19. However, "nitric oxide adduct" cannot include nitrosohemoproteins, as the Examiner assumes, because one of ordinary skill in the art would not be able to make and use S-nitroso-hemoglobin or any other form of nitrosated or nitrated hemoglobin based on these described methods. One of ordinary skill in the art would have no reason to think that any nitrosated or nitrated form of hemoglobin could be made. No information on the stability of any hemoglobin derivative is given, or on its suitability to being used as a coating for a medical device. No person of ordinary skill in the art would be able to carry out any of the methods of Claims 18-21 and 26-30 by looking for guidance in US Patent No. 6,471,978, as it does not have sufficient teachings regarding hemoglobin for anyone to be able to perform any chemical reaction to make any derivatized form of hemoglobin. Further, US 6,471,978 does not have any experimental evidence regarding the biological activity of hemoglobin that has been nitrosated or nitrated.

The Examiner states, without pointing out any specific location in US 6,471,978, ". . . the reference teaches combination of S-nitrosothiols with hemoglobin for their expected NO donating properties and thus would potentiate NO (and oxygen) delivery." Applicant does not find any discussion of a combination of S-nitrosothiols with hemoglobin or any form of S-nitrosohemoglobin in US 6,471,978.

Rejection of Claims 4, 16-19, 21-27 and 29-30 Under 35 U.S.C. § 102(e), or Alternatively, Under U.S.C. § 103 (Item 6 of Office Action)

Claims 4, 16-19, 21-27 and 29-30 have been rejected under 35 U.S.C. § 102(e) as being anticipated, or alternatively, under 35 U.S.C. § 103, as being obvious, over Stamler *et al.*, US 6,153,186.

US Patent Application No. 08/616,255, which issued as US 6,153,186, was filed on the same date as the subject application 08/616,371. Both applications claim the benefit of US Provisional Application No. 60/003,801 filed 15 September 1995. Therefore, US 6,153,186 is not prior art to the subject application 08/616,371.

Rejection of Claims 33-34 Under 35 U.S.C. § 103(a) (Item 7 of Office Action)

Claims 33-34 have been rejected under 35 U.S.C. § 103(a), as they are said to be unpatentable over Stamler *et al.*, WO 93/09806 or US 6,291,424.

US 6,291,424 describes a method that was said to result in SNO-hemoglobin. However, this method is described so incompletely that one of ordinary skill in the art could not follow the protocol. No method of assay is described that could measure whether any SNO-hemoglobin had been formed. The method is merely hypothetical; no evidence is given that SNO-hemoglobin was actually produced, and no physiological effect of SNO-hemoglobin was measured. See the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 mailed to the United States Patent and Trademark Office on February 27, 1998, regarding WO 93/09806, which has the same content as US 6,291,424, except for the claims. See Example 19. See also the Declaration of Joseph Bonaventura Under 37 C.F.R. § 1.132 mailed to the U.S. Patent and Trademark Office on March 12, 1998.

WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin. Therefore, US 6,291,424 also does not present an enabling description of a method to produce S-nitrosohemoglobin. No other reference available at the time of the invention describes a method of producing S-nitrosohemoglobin. Thus, there is no basis for this rejection, either as an anticipation rejection, or as an obviousness rejection.

The Examiner describes in the Office Action the methods for thiol nitrosylation disclosed on pages 30-31 of WO 93/09806:

> 1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic $NaNO_2$ as nitrosating agent in a buffered saline at pH 7.4 for tPA.
> 2. exposure of the protein (e.g. tPA to NO gas in buffered saline)
> With regard to the above, Stamler further notes that other oxides of nitrogen can be utilized (e.g. NOCl, N_2O_3) as well as other nitroso equivalents.

The first method is actually described on page 30 of WO 93/09806 as follows:

> t-PA was first dialyzed against a large excess of 10 mM HCl for 24 hours to remove excess L-arginine used to solubilize the protein. t-PA was then exposed to NO_X generated from equimolar $NaNO_2$ in 0.5 N HCl (acidified $NaNO_2$) or in control experiments, to 0.5 N HCl alone, for 30 minutes at 37° C. Solutions were titrated to pH 7.4 with equal amounts of 1.0 N NaOH and Tris Buffered Saline (TBS), pH 7.4, 0.05 M L-arginine. Dilutions were then made as necessary in TBS.

One of ordinary skill in the art would understand this to mean that the reaction of tPA with acidic $NaNO_2$ was not carried out in buffered saline at pH 7.4, but was carried out in an extremely acidic condition, probably about pH 2.

The second method is described on page 31, lines 7-10 as follows:

> S-NO-t-PA has also been synthesized by exposure of t-PA to NO gas bubbled into buffered (TBS) solution of enzyme. This further illustrates the potential for S-nitrosylation, by exposure of proteins to a variety of oxides of nitrogen including NOCl, N_2O_3, N_2O_4 and other nitroso-equivalents.

No person of ordinary skill in the art would interpret the second sentence above as meaning that "other oxides of nitrogen can be utilized (e.g. NOCl, N_2O_3) [for thiol nitrosylation of proteins] as well as other nitroso equivalents." This sentence does not provide an enabling description of anything.

Example 19 of WO93/09806 and US 6,291,424 has been discussed at length. One of ordinary skill in the art would not find any credible evidence that hemoglobin was nitrosylated on any thiols by SNOAc. Thus, one of ordinary skill in the art would be discouraged from trying any other S-nitrosothiol as a reagent to produce S-nitrosohemoglobin, in excess, or in any ratio to hemoglobin.

The statement the Examiner points out on page 23 to page 24 of WO 93/09806 has nothing to do with the conditions or steps in a method to produce S-nitrosohemoglobin.

The Examiner states,

> It is further noted that the use of higher pH values (e.g. pH 7.4) than that utilized in the thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is also suggested by the reference since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31) and further the reference discloses the use of pH 7.4 in the making and storage of various thiol proteins. Additionally, the thiol-protein synthetic steps are analogous to that of Example 19: see page 30, lines 20-27; page 33, lines 20-26).

The reported stability of S-NO-t-PA in storage conditions at pH 7.4 does not reveal anything about the reaction conditions under which it can be made. WO 93/09806 does not disclose the use of pH 7.4 in any attempts to produce any S-nitrosoproteins. One of ordinary skill in the art is left with much more than mere optimization of conditions.

Provisional Rejection of Claims 16-21 and 26-30 For Obviousness-Type Double Patenting (Item 9 of Office Action)

Claims 16-21 and 26-30 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable "over claims 1-17 (especially claims 7-9 and 17)" of copending Application No. 10/216,865 (PG Pub. US 2003/007967 A1).

The Examiner has not set forth the rejection with sufficient particularity that Applicant can be expected to understand how each of Claims 16-21 and 26-30 are not patentably distinct from each of Claims 1-17 of copending Application No. 10/261,865. The Examiner has given, in effect, 187 bases for rejection in concluding that the rejected claims are unpatentable over Claims 1-17 of copending Application No. 10/216,865.

Section 804 of the *Manual of Patent Examining Procedure* (MPEP) gives guidance on determining whether a nonstatutory basis exists for a double patenting rejection. Page 800-22 of the MPEP (8th edition, revised February, 2003) states:

> Any obviousness-type double patenting rejection should make clear:
>
> (A) The differences between the inventions defined by the conflicting claims -- a claim in the patent compared to a claim in the application; and
>
> (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent.

The Examiner has not made clear the differences between each of the rejected claims and each of the 17 claims of copending Application No. 10/216,865 to which each of the rejected claims are being compared, and the reasons why a person of ordinary skill in the art would conclude that the invention defined in each of rejected Claims 16-21 and 26-30 is an obvious variation of the invention defined in each of Claims 1-17 of copending Application No. 10/216,865. The Examiner only includes a brief general discussion, including discussion of composition claims to S-nitrosohemoglobin. Neither the subject patent application nor the reference patent application contains claims to S-nitrosohemoglobin.

The inventors listed on the face of Pub. No. US 2003/000796 are Jonathan Stamler, Joseph Loscalzo, Daniel Simon and David J. Singel. The United States Patent and Trademark Office erred in listing Jonathan Stamler as an inventor. 37 C.F.R. § 1.63 requires, *inter alia*:

> (a) An oath or declaration filed under § 1.51(b)(2) as a part of a nonprovisional application must:
>
> (4) State that the person making the oath or declaration believes the named inventor or inventors to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought.

Jonathan S. Stamler has not signed a Declaration of Inventorship in US Patent Application No. 10/216,865 (PG Pub. US 2003/0007967) because he is not an inventor. Dr. Stamler cannot be assumed to be an inventor of the claims of 10/216,865 from any other circumstances. Because Jonathan S. Stamler is not an inventor of Claims 1-17 of US Patent Application No. 10/216,865, there is no common inventor between the instant application and US Patent Application No. 10/216,865, and no double patenting rejection can apply.

Rejection of Claims 16-21 and 26-30 For Obviousness-Type Double Patenting (Item 10 of Office Action)

Claims 16-21 and 26-30 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-4 of US 6,583,113.

Claims 1-4 of US 6,583,113 are drawn to methods comprising delivering nitric oxide to a targeted site in the body of a patient from a nitrosated and/or nitrosylated heme protein, wherein the heme protein is nitrosated and/or nitrosylated at one or more thiol groups in the heme protein. Claim 1 encompasses "treating or preventing a disease or disorder in a patient." However, the meaning and scope of Claims 1-4 are unclear, because it is not required that any treatment be performed on the patient, for example, administering a pharmaceutical substance. Claims 1-4 of US 6,583,113 do not comprise a step of administering to a mammal or to a human any preparation comprising SNO-hemoglobin. Because the step of the method is different, Claims 16-21 and 26-30 are patentably distinct from Claims 1-4 of 6,583,113. Claims 1-4 of US 6,583,113 read on a process that occurs in nature. It is known that SNO-hemoglobin, which delivers nitric oxide to sites in the body, occurs naturally in red blood cells. See Table 2 on page 66 of the specification of 08/616,371, and Jia, L. *et al.*, *Nature380*:221-226 (1996).

The Examiner has not set forth the rejection with sufficient particularity that Applicant can be expected to understand how each of Claims 16-21 and 26-30 are not patentably distinct from each of Claims 1-4 of US 6,583,113. The Examiner has given, in effect, 44 bases for rejection in concluding that the rejected claims are unpatentable over Claims 1-4 of US 6,583,113.

Section 804 of the *Manual of Patent Examining Procedure* (MPEP) gives guidance on determining whether a nonstatutory basis exists for a double patenting rejection. Page 800-22 of the MPEP (8th edition, revised February, 2003) states:

> Any obviousness-type double patenting rejection should make clear:
>
> (A) The differences between the inventions defined by the conflicting claims -- a claim in the patent compared to a claim in the application; and
>
> (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is

> an obvious variation of the invention defined in a claim in the patent.

The Examiner has not made clear the differences between each of the rejected claims and each of the four claims of US 6,583,113 to which each of the rejected claims are being compared, and the reasons why a person of ordinary skill in the art would conclude that the invention defined in each of rejected Claims 16-21 and 26-30 is an obvious variation of the invention defined in each of Claims 1-4 of US 6,583,113. It is unclear what meaning Claims 1-4 of US 6,583,113 can have, as there is no demonstration in the patent that a heme protein of any kind can deliver nitric oxide to any site in the body. The Examiner only includes a brief general discussion, including discussion of composition claims to S-nitrosohemoglobin. Neither the subject patent application nor US 6,583,113 contain composition claims to S-nitrosohemoglobin.

The parent application to US 6,583,113 is 09/092,622 (now US Patent No. 6,291,424). Applicant requests that the Examiner consider the file history of the parent application to the cited patent US 6,583,113. The inventors listed on the face of US 6,291,424 are Johnathan [sic] Stamler, Joseph Loscalzo and David J. Singel. The United States Patent and Trademark Office erred in listing Jonathan Stamler as an inventor. 37 C.F.R. § 1.163 requires, *inter alia*:

> (a) An oath or declaration filed under § 1.51(b)(2) as a part of a nonprovisional application must:
>
> (4) State that the person making the oath or declaration believes the named inventor or inventors to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought.

The file history of US 6,291,424 (specifically, papers submitted as exhibits with a Petition Under 37 C.F.R. § 1.47(a) and Declarations in Support of Filing Under 37 C.F.R. § 1.47(a) filed on December 30, 1998 for 09/092,622) shows that Dr. Stamler did not sign a Declaration of Inventorship for that application because he did not believe the named inventors to be the original and first inventors of the subject matter claimed in the application. See Exhibit P, a copy of "Declaration of Gretchen A. Rice in Support of Filing Under 37 C.F.R. § 1.47(a)" mailed to the United States Patent and Trademark Office on 30 December 1998 for Patent Application No.

09/092,622. Also see Exhibit Q (referred to as Exhibit G in the Declaration of Gretchen A. Rice) a copy of a letter from Maxim H. Waldbaum, Esq. of Sidley & Austin to Gretchen A. Rice, Esq., attorney of record for Patent Application No. 09/092,622, dated December 16, 1998. However, in spite of the requirements of 37 C.F.R. § 1.63, the United States Patent and Trademark Office granted the Petition and granted the application Rule 1.47(a) status.

The Senior Legal Advisor who drafted the Decision on the Petition was apparently persuaded by the argument made by the attorney for applicants of 09/092,622 that its specification "is identical to the specification of USSN 07/943,835." Apparently, the attorney for applicants of 09/092,622 was referring to the written sections of the application excluding the claims. The claims are in fact part of the specification. Therefore, it is not true that the specification of the patent application that became US 6,292,424 is identical to the specification of its parent application, 07/943,835.

The attorney for applicants of 09/092,622 brought up repeatedly in the Declaration in Support of Filing Under 37 C.F.R. § 1.47(a) the fact that Dr. Stamler had previously executed an assignment to Brigham and Women's Hospital for US Patent Application No. 07/943,835 in 1992. However, 37 C.F.R. § 1.63 does not recognize, and no other statute in patent law recognizes any obligation that allegedly results from the signing of an assignment in a related application. Note that 37 C.F.R. § 1.63(a)(4) requires that all named inventors believed the named inventors to be the original and first inventors "*of the subject matter which is claimed and for which a patent is sought.*" The subject matter of the claims in 09/092,622 was different from the subject matter of the claims of prior applications. It should be noted that Application No. 09/092,622 (US 6,291,424) is listed on the face of the 6,291,424 patent as being a continuation-in-part of Application No. 08/409,720 (filed March 24, 1995), which is a continuation-in-part of 08/198,854 (filed February 17, 1994), which is a divisional of 07/943,835 (filed September 14, 1992). The filing of 09/092,622 as a continuation-in-part rather than a continuation application is an acknowledgment that its claims are different from those of previously filed applications to which it claims priority. The signing of the assignment in 07/943,835 should not carry any weight; it does not state anything about the signatory's belief as to who invented the subject matter of the claims.

Copies of the papers in the parent application 09/092,622 – the Petition Under 37 C.F.R. § 1.47(a), Declarations in Support of Filing Under 37 C.F.R. § 1.47(a) and exhibits accompanying the Declarations – were submitted with Patent Application No. 09/835,038 (US Patent No. 6,583,113) upon its filing on April 16, 2001. Status as an application under 37 C.F.R. § 1.47(a) was again granted by the Patent Office to 09/835,038, thereby repeating the mistake in the parent application 09/092,622.

Because Jonathan S. Stamler is not an inventor of Claims 1-4 of US Patent No. 6,583,113, there is no common inventor between the instant application and US Patent No. 6,583,113, and no double patenting rejection can apply.

Rejection of Claims 16-21 and 26-30 For Obviousness-Type Double Patenting (Item 11 of Office Action)

Claims 16-21 and 26-30 have been rejected under the judicially created doctrine of obviousness-type double patenting, as they are said to be unpatentable over Claims 1-65 of US 6,471,978, "as interpreted in light of the specification regarding the scope and treatment of vasculature damage and inherency." The Examiner is requested to clarify how the disclosure is being used and exactly what is said to be inherent, in reference to specific claims.

The Examiner has not set forth the rejection with sufficient particularity that Applicant can be expected to understand how each of Claims 16-21 and 26-30 are not patentably distinct from each of the 65 claims of the patent. The Examiner has given, in effect, 715 bases for rejection in concluding that the rejected claims are unpatentable over Claims 1-65 of US Patent No. 6,471,978.

Section 804 of the *Manual of Patent Examining Procedure* (MPEP) gives guidance on determining whether a nonstatutory basis exists for a double patenting rejection. Page 800-22 of the MPEP (8th edition, revised February, 2003) states:

> Any obviousness-type double patenting rejection should make clear:
>
> (A) The differences between the inventions defined by the conflicting claims – a claim in the patent compared to a claim in the application; and

> (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent.

The Examiner has not made clear the differences between each of the rejected claims and each of the 65 claims of US Patent No. 6,471,978 to which each of the rejected claims are being compared, and the reasons why a person of ordinary skill in the art would conclude that the invention defined in each of rejected Claims 16-21 and 26-30 is an obvious variation of the invention defined in each of Claims 1-65 of the patent. The Examiner instead includes a general discussion of the teachings of the patent, not an analysis of the claims. The Examiner includes discussion of "present claims directed to 'potentiation of NO delivery.' " There are no claims like this in the subject patent application.

The Examiner discusses an interpretation of the teachings of Stamler *et al.* (US 6,471,978) in columns 1-4. The Examiner is requested to clarify how this is being applied to the rejection. Which claim or claims of US 6,471,978 are supported by the disclosure in columns 1-4, and to which claim or claims of the subject patent application is this relevant? Columns 1 and 2, and column 3, lines 1-43 are not new teachings of the patent, but are prior art teachings in the "Background of the Invention" section.

The Examiner seems to conclude that one of ordinary skill in the art could extrapolate from the claims of US 6,471,978 that SNO-hemoglobin should be administered to a mammal or a human for producing the effects of nitric oxide. The method of Claims 1-65 is narrow in scope, requiring a damaged vascular surface. The methods of Claims 16-21 and 26-30 of the subject patent do not require the presence of damaged vascular surface for the hemoglobin derivatives to be applied. The class of agents in Claims 1-65 of US 6,471,978 is extremely broad and includes compounds with no demonstrated ability to release NO. It is not true, as the Examiner states, that "the same protein is applied in the same way in the same amount." In all of Claims 1-65 of US Patent No. 6,471,978, the method is to apply to a damaged vascular surface a nitric oxide adduct. In all of the claims of the subject patent application, the method is to administer to a mammal or human a composition comprising SNO-hemoglobin.

It is not apparent to one of ordinary skill in the art why agents that must be applied to a damaged vascular surface for the purpose of treating that damaged vascular surface, and are not effective if administered systemically (see Figure 3 and column 28, line 58 to column 29, line 3), would have any effect on disease conditions in a mammal or human. For this reason, Claims 15-21 and 26-30 of the subject patent application are distinct from all the claims of US 6,471,978, and Claims 16-21 and 26-30 of the subject patent application are not obvious variations of the subject matter of the claims of US 6,471,978.

SNO-hemoglobin was not known to exist before the filing of the priority application for the subject application. For this reason alone, Claims 16-21 and 26-30 of the subject patent application are distinct from the claims of US 6,471,978, and cannot be an obvious variation of the claims of US 6,471,978.

The Examiner states, "The selection of 'nitric oxide adducts' of hemoglobin (e.g. (S) nitrosated/nitrated polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment) 'nitric oxide adduct' i.e. includes nitrosohemoglobins, with hemoglobin being preferred." The Examiner is requested to clarify this statement. To which claim of the application does it refer, and to which claim of the cited patent does it refer? What meaning does "is anticipated or in the alternative obvious" have in the context of an obviousness-type double patenting rejection? The case referred to [*In re Schaumann*, 197 USPQ 5 (CCPA1978)] has as its issue the question of whether the disclosure of a chemical genus may ever constitute a description of a specific compound falling within the ambit of the genus. The court concluded that the claimed species was obvious in view of the small recognizable class of compounds disclosed in the prior art reference, under 35 U.S.C. § 102(b). Applicant does not see the relevance of *In re Schaumann*. The claims of US 6,471,978 do not include any well-defined chemical genus.

The Examiner states, "The prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I., 1993)." Using the patent disclosure as though it were prior art is impermissible in a double patenting rejection. See *In re Kaplan*, 229 USPQ 678, 683 (Fed. Cir. 1986).

Rejection of Claims 4, 16-19, 21-27 and 29-30 For Obviousness-Type Double Patenting (Item 12 of Office Action)

Claims 4, 16-19, 21-27 and 29-30 have been rejected under the judicially created doctrine of obviousness-type double patenting "as being unpatentable over claims 1-14 of Stamler *et al.* US Pat. No. 6,153,186 (11/00: effectively filed 9/95 by 60/003,801) as interpreted in light of the patent specification regarding the scope of treatment of a mammal in need thereof (e.g., patent claims 8-9) and inherency."

The Examiner also uses the language of rejections under 35 U.S.C. § 102 and 35 U.S.C. §103: "The reference anticipates or in the alternative renders obvious direct as well as indirect (through cell delivery) administration of S-nitrosothiols." Reference is made to *In re Schaumann*, 197 USPQ 5 (CCPA 1978) which has as its issue the question of whether the disclosure of a chemical genus may ever constitute a description of a specific compound falling within the ambit of the genus. The court concluded that the claimed species was obvious in view of the small recognizable class of compounds disclosed in the prior art reference, under 35 U.S.C. § 102(b). Applicant does not see the relevance of *In re Schaumann.* The claims of US 6,153,186 do not include any well-defined chemical genus. Applicant assumes that the rejection has been made under obviousness-type double patenting, in spite of the confusing language.

The Examiner has not set forth the rejection with sufficient particularity that Applicant can be expected to understand how each of Claims 4, 16-19, 21-27 and 29-30 are not patentably distinct from each of Claims 1-14 of US Patent No. 6,153,186. The Examiner has given, in effect, 196 bases for rejection in concluding that the rejected claims are unpatentable over Claims 1-14 of US Patent No. 6,153,186.

Section 804 of the *Manual of Patent Examining Procedure* (MPEP) gives guidance on determining whether a nonstatutory basis exists for a double patenting rejection. Page 800-22 of the MPEP (8th edition, revised February, 2003) states:

> Any obviousness-type double patenting rejection should make clear:
>
> (A) The differences between the inventions defined by the conflicting claims -- a claim in the patent compared to a claim in the application; and
>
> (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is

> an obvious variation of the invention defined in a claim in the patent.

The Examiner has not made clear the differences between each of the rejected claims and each of the 14 claims of US Patent No. 6,153,186 to which each of the rejected claims are being compared, and the reasons why a person of ordinary skill in the art would conclude that the invention defined in each of rejected Claims 4, 16-19, 21-27 and 29-30 is an obvious variation of the invention defined in each of Claims 1-14 of US Patent No. 6,153,186. The Examiner only includes a brief general discussion of the teachings of the disclosure, without analyzing the claims. It is impermissible to use the patent disclosure as prior art in an obviousness-type double patenting rejection. See *In re Kaplan*, 229 USPQ 678, at 683 (Fed. Cir. 1986).

The claims of US Patent No. 6,153,186 are drawn to a method comprising a step of incubating *red blood cells* with one or more nitrosothiols. None of the claims of the subject patent application include a step similar to this, or any step using *red blood cells*. For this reason, Claims 4, 16-19, 21-27 and 29-30 of the subject application are certainly patentably distinct from the claims of US 6,153,186.

Rejection of Claims 16-21 and 26-30 Under 37 C.F.R. § 1.78(b) (Item 13 of Office Action)

Claims 16-21 and 26-30 have been rejected under 37 C.F.R. § 1.78(b), as they are said to "conflict with claims which are present in Application No. 08/667,003 and 08/796,164." 37 C.F.R. § 1.78(b) is as follows:

> (b) Where two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application.

Application No. 08/667,003 issued as US 6,197,745 on March 6, 2001, so the provisions of 37 C.F.R. § 1.78(b) do not apply, as 08/667,003 is no longer an application. However, the claims of both US 6,197,745 and US Patent Application No. 08/796,164 have been reviewed for conflicting claims. The claims were found to differ in scope and meaning from the claims of the subject application.

The Examiner is asked to identify with particularity those claims in the cited patent and patent application that conflict with Claims 16-21 and 26-30 of the subject patent application, and to provide the reasoning for those conclusions.

CONCLUSION

The Examiner is requested to consider the above remarks, and withdraw the rejections. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Carol A. Egner

Carol A. Egner
Registration No. 38,866
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: May 17, 2004

PATENT
Attorney Docket No: 102258.262

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: **Stamler, et al.**

Serial No.: **09/092,622**

Filed: **June 5, 1998**

For: **NITROSATED AND NITROSYLATED HEME PROTEINS**

Assistant Commissioner for Patents
Washington, D.C. 20231

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington D.C. 20231.
on Dec. 30, 1998
(Date of Deposit)
Karen Kenney
Person Making Deposit
Karen Kenney
Signature

DECLARATION OF GRETCHEN A. RICE
IN SUPPORT OF
FILING UNDER 37 C.F.R. §1.47(a)

Sir:

The undersigned, Gretchen A. Rice, declares and states that:

1. I am an attorney of record for the above-identified patent application.

2. I am making this declaration based on first-hand knowledge of the facts surrounding the refusal of one of the joint inventors, Dr. Jonathan Stamler, to sign the Combined Declaration for Patent Application and Power of Attorney and Assignment for this application.

3. The above-referenced application is a: continuation-in-part of USSN 08/409,720, filed March 24, 1995, now abandoned, which is a continuation-in-part of 08/198,854, filed February 17, 1994, now abandoned, which is a divisional of 07/943,835, filed September 14, 1992, now abandoned, which is a continuation-in-part of 07/791,668, filed November 15, 1991, now abandoned.

4. The specification of the above-referenced application is **identical** to the specification of USSN 07/943,835 and the claims of the above-referenced application are supported by the specification. The inventors of USSN 07/943,835, one of whom

EXHIBIT
tabbies
P

was Dr. Stamler, executed an assignment on October 30, 1992 which assigned their entire right, title and interest in and to the invention to Brigham and Women's Hospital. Exhibit A is a copy of the assignment for USSN 07/943,835.

5. On or about December 13, 1993, Dr. Stamler left the employment of Brigham and Women's Hospital and took a position at Duke University, his present employer.

6. Exhibit B is a copy of a letter dated November 20, 1998 to Maxim H. Waldbaum, Esq., attorney for Duke University, from Gretchen A. Rice, requesting that he obtain the signature of Dr. Stamler on the Combined Declaration and Assignment. The letter explains that the specification of the above-referenced application is **identical** to the specification of a USSN 07/943,835, filed September 14, 1992, for which Dr. Stamler executed an assignment on October 30, 1992. A copy of the specification and claims for the above referenced application, a copy of the specification and claims for USSN 07/943,835, and a copy of the assignment for USSN 07/943, 835 were all included with the November 20, 1998 letter.

7. Exhibit C is a copy of a facsimile letter from Maxim H. Waldbaum, Esq., dated November 24, 1998, stating among other things that "we will examine the entire file entire histories in the chain of this application before we answer you" and requesting a copy of all continuing prosecution not previously provided should be sent to him.

8. Exhibit D is a copy of my facsimile letter to Mr. Waldbaum, dated November 30, 1998, in which, among other things, I reiterated that Dr. Stamler was being asked to comply with the terms of his executed assignment and to execute a new assignment for the above-referenced patent application which was **identical** to USSN 07/943,835 for which Dr. Stamler had previously executed an assignment.

9. Exhibit E is a copy of a facsimile letter from Mr. Waldbaum, dated November 30, 1998, which replied to my letters of November 20 and 30, 1998 and to a letter regarding two other matters dated November 23, 1998. In his November 30, 1998 letter, Mr. Waldbaum stated among other things that "we will attempt to provide to

you a more detailed response to your November 20, 23 and 30, 1998 letters" (see page 2 of the letter in exhibit E) and requesting a copy of the pending claims corresponding to the applications.

10. Exhibit F is a copy of my facsimile letter to Mr. Waldbaum, dated December 2, 1998, except that the text of the letter which is directed at two unrelated matters has been redacted. In my December 2, 1998 letter, I stated among other things that the claims pending in the above-referenced application were provided with the letter of November 20, 1998. I also reiterated for the third time that Dr. Stamler was being asked to execute an assignment for the above-referenced patent application the specification of which application is **identical** to the specification of USSN 07/943,835, and reminding Mr. Waldbaum that Dr. Stamler previously executed an assignment to the Brigham and Women's Hospital for USSN 07/943,835.

11. Exhibit G is a copy of a facsimile letter from Mr. Waldbaum, dated December 16, 1998, except that the text of the letter which is directed at two unrelated matters has been redacted. In his December 16, 1998 letter, Mr. Waldbaum states, among other things, that Dr. Stamler believes that named inventors for the above-referenced application are not the proper inventors as Dr. Stamler believes that while working at Duke University he completed the work which he feels enables the claimed invention. Thus, Mr. Waldbaum asserts that Dr. Stamler is legally obligated to refuse to execute both of the Combined Declaration and Assignment.

12. Exhibit H is a copy of my facsimile letter to Mr. Waldbaum, dated December 19, 1998, in which I state among other things that the claims of the above-referenced application were fully enabled by the specification of USSN 07/943,835 to which the specification of the above-referenced application is identical, and that Mr. Waldbaum's letters would be submitted to the Patent Office as evidence of Dr. Stamler's refusal to execute the Combined Declaration and the Assignment.

13. On information and belief, Dr. Stamler has not signed the Combined Declaration or Assignment for the above-referenced patent application.

14. On information and belief, filing under 37 C.F.R. §1.47(a) is necessary to preserve the rights of the assignee, Brigham and Women's Hospital.

15. I declare further that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further that the statements are made with the knowledge that wilful false statements and the like are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardize the validity of the patent application or any patent issuing thereon.

Respectfully submitted,

Dated: December 19, 1998

Gretchen A. Rice

Gretchen A. Rice, Ph.D.
Registration No. 37,429
Hale and Dorr LLP
60 State Street
Boston, Massachusetts 02109
Tel. No.: (617) 526-6000

/netuser13/rice/op/102258.262/1_47decl.wpf

PATENT
Attorney Docket No: 102258.262

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: **Stamler, et al.**

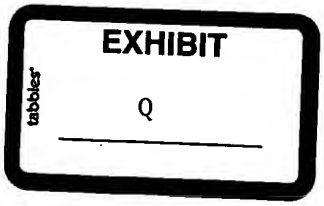
Serial No.: **09/092622**

Filed: **June 5, 1998**

For: **NITROSATED AND NITROSYLATED HEME PROTEINS**

Assistant Commissioner for Patents
Washington, D.C. 20231

EXHIBIT G



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WRITER'S DIRECT NUMBER
(212) 906-2343

WRITER'S E-MAIL ADDRESS
mwaldbau@sidley.com

December 16, 1998

By Facsimile (w/o enclosures)
Confirmation by Federal Express (w/ enclosures)

Gretchen A. Rice, Esq.
Hale and Dorr LLP
60 State Street
Boston, Massachusetts 02109

Re: Jonathan Stamler et al., U.S. Application No. 09/092,622 entitled Nitrosated and Nitrosylated Heme Proteins - Your Ref. - 102258.262; and U.S. Application Nos. 08/438,418 and 08/460,465, entitled Localized Use of Nitric Oxide Adducts to Prevent Internal Tissue Damage - Your Refs.: 102258.210 and 102258.214

Dear Gretchen:

Further to our November 30, 1998 letter, the following is a detailed response to your letters of November 20, 23, 30 and December 2, 1998.

U.S. Application No. 09/092,622

Dr. Stamler not only has a legal right to refuse to sign the combined Declaration/Power of Attorney corresponding to U.S. Application No. 09/092,622 ('622), he is in fact legally prohibited from signing this document. 37 C.F.R. §1.63[1] prohibits Dr. Stamler from signing this combined Declaration/Power of Attorney because Dr. Stamler maintains that the inventors named in this declaration are not the original and first inventors of the subject matter which is claimed and for which a patent is sought.

The claims of the '622 Application are not enabled by its written description which is identical to that of the parent application, U.S. Application No. 07/943,835, filed September 14, 1992. The teaching in this application and the specification at pages 1-59 or figures 1-30 do not

[1] 37 C.F.R. §1.63(b) (1998) requires that "the oath or declaration must state that the person making the oath or declaration . . . [b]elieves the named inventor or inventors to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought."

show enablement for the broad claims as stated for a compound comprising a thiol containing heme protein and an NO or NO_2 group which is directly or indirectly linked to said thiol. For example, the description of S-nitrosylation of hemoglobin at pages 19-20 and 58-59 and figures 28 and 29 does not actually enable production of S-NO-Hemoglobin. In fact, the work which enables the claimed subject matter of this application was completed by Dr. Stamler at Duke University several years after the parent application was filed. The Brigham's filing of the '622 application is an attempt to appropriate subject matter invented by Dr. Stamler at Duke University. Accordingly, because Dr. Stamler maintains that the inventors named on this declaration did not invent the subject matter claimed, he has every right and is in fact legally obligated to refuse to sign the combined Declaration/Power of Attorney corresponding to the '622 application.

For the reasons stated above, Dr. Stamler is also prohibited from signing the Assignment corresponding to the '622 Application. Because Dr. Stamler maintains that the inventors named on the subject application did not invent the claimed subject matter, he cannot swear, as the Assignment requires, that the named inventors for the subject application have full right to convey the entire interest of the application. Moreover, as we have stated in past correspondence with The Brigham and Nitromed, The Brigham possesses no rights in subject matter invented by Dr. Stamler *after* Dr. Stamler terminated his relationship with the Brigham. Accordingly, Dr. Stamler has every right and is in fact legally obligated to refuse to sign the Assignment corresponding to the '622 Application.

U.S. Application Nos. 08/438,418 and 08/460,465

SIDLEY & AUSTIN NEW YORK

Gretchen A. Rice, Esq.
December 16, 1998
Page 4

Please contact me if you have any questions or wish to discuss this matter further.

Sincerely,

Maxim H. Waldbaum

TAH:jf
Enclosures

cc: Dr. Robert L. Taber (w/o enclosures)
Dr. Jonathan Stamler (w/o enclosures)

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